Serotonin nerve cells in Alzheimer's disease

Sir: A recent report\(^1\) showing that the uptake of serotonin (5HT) by neocortical biopsy tissues is significantly reduced in patients with Alzheimer's disease (AD) implies that there may also be damage to the 5HT-containing nerve cells, situated in the raphe nuclei of the brain stem and mid brain,\(^2\) in this condition. We have examined those nerve cells which lie in the caudal part of the mesencephalon and upon the medial and dorsal surfaces of the medial longitudinal fasciculus, and which are variously known as the nucleus supratrochlearis,\(^3\) or dorsal tegmental nucleus (DTN).\(^4\) These together with neurons of the nucleus dorsalis raphe and nucleus centralis superior make up\(^5\) the 5HT-containing nerve cells of the upper brain stem. Changes in their structure are sought and capacity for function is assessed by measurement of nucleolar volume and cytoplasmic RNA content.\(^6\)

Brains were obtained at necropsy from 15 histologically confirmed cases of AD (age 77-4 ± 1.8 years; postmortem delay 35-4 ± 6.5 hours) and nine controls of similar age (79-6 ± 1.2 years; postmortem delay 36-9 ± 3.7 hours) dying without neurological or psychiatric disease and judged to be mentally preserved. Immediate cause of death was similar in both groups, being associated with bronchopneumonia or cardiac insufficiency. Paraffin sections cut at a thickness of 16 \(\mu\)m from blocks of pons (at level of nucleus of IV cranial nerve) were stained for RNA.\(^7\) Nucleolar volume and cytoplasmic RNA content were measured\(^8\) in 30 cells of the medial and lateral divisions of DTN\(^9\) in all 24 cases. In most of the patients with AD globose neurofibrillary tangles occupying much of the nerve cell perikaryon were common (fig) in both divisions, though senile plaques were not seen. The table shows that, when compared with controls, nucleolar volume and cytoplasmic RNA content are significantly reduced (p < 0.001 in each instance) in AD, by 31 and 38% respectively, in both medial and lateral divisions of DTN. The changes in cell structure (tangle formation) together with a reduced functional capacity probably form the basis for the altered 5HT metabolism, reported at necropsy,\(^7\) or within the living patient,\(^10\) with AD.

The impaired functioning, in AD, of other groups of neurons, such as the cholinergic cells of the basal forebrain (substantia innominata)\(^11\) and the noradrenergic cells of the locus caeruleus,\(^12\)-\(^14\) which also give rise to pathways projecting to the neocortex, indicates that the changes in 5HT, may therefore be yet another aspect of a widespread process of deprivation of cortical input. Furthermore, these additionally damaged serotonergic and noradrenergic systems may be part of the reason as to why those therapeutic measures aimed at restituting the cholinergic system alone, have met with only limited success.

David MA Mann
Peter O Yates
Department of Pathology
The University
Manchester
M13 9PT, UK

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References


Fig. Section of dorsal tegmental nucleus (see text).

Table Nucleolar volume and cytoplasmic RNA content of nerve cells of dorsal tegmental nucleus in Alzheimer's disease patients and controls

<table>
<thead>
<tr>
<th>Nucleolar volume ((\mu)m(^3))</th>
<th>Medial DTN</th>
<th>Lateral DTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease (n = 15)</td>
<td>22.9 ± 1.0*</td>
<td>23.0 ± 1.0*</td>
</tr>
<tr>
<td>Controls (n = 9)</td>
<td>33.2 ± 0.9</td>
<td>33.2 ± 0.9</td>
</tr>
<tr>
<td>RNA content (AU)</td>
<td>Medial DTN</td>
<td>Lateral DTN</td>
</tr>
<tr>
<td>Alzheimer's disease (n = 15)</td>
<td>20.9 ± 0.8*</td>
<td>21.0 ± 0.7*</td>
</tr>
<tr>
<td>Controls (n = 9)</td>
<td>33.7 ± 1.1</td>
<td>34.1 ± 0.8</td>
</tr>
</tbody>
</table>

AU = arbitrary units
* at least < 0.001 from control value (Student t test)
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D M Mann and P O Yates

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